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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,581	01/23/2004	Steven N. Mink	82402-10302	3020

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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,581	MINK ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,13-16 and 19-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-6,13,14,16 and 22-24* is/are rejected.

7)☒ Claim(s) *15 and 19-21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted March 30, 2007 wherein claims 1 and 16 are amended, claims 7-12 are cancelled, and new claims 17-22 are introduced. This application claims benefit of provisional application 60/442060, filed January 24, 2003.

Claims 1-6, 13-16, and 19-24 are pending in this application.

Claims 1-6, 13-16, and 19-24 as amended are examined on the merits herein.

All rejections of record in the previous office action are withdrawn. The following new grounds of rejection are introduced:

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

In the instant case, new claims have been introduced having the same numbering as cancelled claims 17 and 18. Misnumbered claims 17-22 have been renumbered 19-24.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 6, 13, 14, 16, and 22-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method involving administering N-acetylglucosamine-containing carbohydrates, or an antisense oligonucleotide or antibody to lysozyme, does not reasonably provide enablement for a method involving administering any inhibitor of lysozyme whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a therapeutic method involving administering a compound to a subject. In order for the invention to be enabled, the specification must allow one of ordinary skill in the art to make and use the invention for each and every embodiment included within the scope of "an agent that can inhibit lysozyme."

The state of the prior art: Lysozyme is known in the art to be a marker of sepsis and systemic inflammatory response. It is not known in the art as a therapeutic target for he treatment of these diseases.

While a number of inhibitors of lysozyme are known in the art, the full range of all possible inhibitors of lysozyme is not known. The art also does not provide any method for discovering or producing all possible inhibitors of lysozyme.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Targeting lysozyme for the treatment of myocardial dysfunction in sepsis and SIRS is a new therapeutic strategy which has not been characterized to the extent that would render the discovery of new active agents routine and predictable.

Furthermore, because of the diversity of possible chemical substances in existence and the unpredictability of the biological properties of novel chemical substances, it is highly unpredictable which novel compounds will be discovered to be inhibitors of lysozyme and what synthetic strategies can be used to produce these compounds.

The Breadth of the claims: The claimed invention is very broad, including methods of administering any compound whatsoever that happens to inhibit lysozyme, to a subject suffering from sepsis or systemic inflammatory response.

The amount of direction or guidance presented: Pp. 15-23 of the instant specification disclose various classes of compounds, such as certain carbohydrates, antibodies, or oligonucleotides. The specification does not disclose any method for

determining the full scope of all possible lysozyme inhibitors beyond those falling within these particular classes, or a method of making these molecules.

The presence or absence of working examples: Several working examples are provided in the specification demonstrating specific compounds, such as N,N',N'' triacetylglucosamine, that are useful in the claimed method. The working examples provided are not representative of the full scope of all possible compounds that could inhibit lysozyme.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the discovery of novel therapeutic agents. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of lysozyme inhibitors beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is useful as an inhibitor of lysozyme. According to the 2006 Chemical Abstracts catalog, (Reference included with PTO-892) The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to have lysozyme inhibitory activity. For most compounds, it is unknown whether they are or are not useful as lysozyme inhibitors. Gathering this data for every compound known to man would involve *in vitro* screening of an enormous diversity of chemical compounds for lysozyme inhibitory activity, as well as *in vivo* testing of compounds having this activity involving either human or animal subjects to determine

therapeutic utility. *In vitro* testing requires that the compounds to be tested be synthesized and subjected to an appropriate screening method. As described earlier, synthesis of diverse chemical structures requires novel and unpredictable experimentation in order to develop suitable synthetic methods. *In vivo* animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential lysozyme inhibitors, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, dissection, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible lysozyme inhibitor, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of lysozyme inhibitors claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for all possible lysozyme inhibitors.

Claims 1-6 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating sepsis or SIRS, or of reversing or reducing myocardial depression, does not reasonably provide enablement for a method of preventing myocardial dysfunction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is drawn to a therapeutic method for treatment or prevention of a disorder. Prevention is interpreted to mean the

complete blocking of all symptoms or effects of the disorder for an indefinite period of time.

The state of the prior art: Lysozyme is known in the art to be a marker of sepsis and systemic inflammatory response. It is not known in the art as a therapeutic target for he treatment of these diseases.

In general, prevention of any disorder in the sense being used herein is not a recognized clinical outcome in the art, as no treatment is perfectly effective. The state of the art in so-called "preventative" medicine involves merely reducing the likelihood and/or severity of the disorder being prevented.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Prevention of a disease is not the same as treatment of said disease. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely

suppress all symptoms? For example, will a metastatic cancer eventually adapt to overcome treatments directed to preventing it from metastasizing?

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

Additionally, in the case of myocardial dysfunction related to systemic inflammation, the underlying cause is a challenge with an exogenous inflammatory agent, such as a pathogenic microorganism. The introduction of invasive microorganisms into the body is unpredictable, as it is not possible to predict when an individual will encounter such microorganisms and suffer infection. Therefore treatment cannot necessarily be administered before the onset of sepsis if the occurrence of sepsis cannot be predicted. Rather, treatment is administered to a patient who has already developed a systemic inflammatory response, in order to treat, reduce, or reverse the effects of the disorder rather than actually preventing it.

For this reason, many therapies which are suitable for short-term relief of symptoms are not suitable for lifelong prevention of disease. For example, antibiotics, chemotherapeutics, and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The Breadth of the claims: In the absence of an explicit definition in Applicant's specification, "Prevention" as recited in the instant claims, is interpreted to mean the

complete and total blocking of all symptoms of a disorder for an indefinite period of time. Any therapy which merely reduces the number or severity of symptoms, or which is effective for a period shorter than the subject's remaining lifespan, is considered to be ineffective at preventing a disorder.

The amount of direction or guidance presented: No guidance is given in the specification suggesting any reason to believe that administration of an inhibitor of lysozyme can achieve complete prevention of myocardial dysfunction.

The presence or absence of working examples: No working examples are given for prevention of disease.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of disease. See MPEP 2164.

The quantity of experimentation necessary: As mentioned above, the short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness for prevention of disease. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy. In particular, one skilled in the art, in order to practice the invention for prevention of disease, would need to know whether the preventative effect remains potent over the long term.

In order to answer these questions in the absence of any existing data, one skilled in the art, in order to practice the invention, would undertake long-term animal

tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or monkeys, or a human clinical trial. Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Administering the claimed compounds for a period of years to a suitable subject population is an undue amount of experimentation needed in order to practice the full range of the claimed invention. As prevention in the full sense is an extremely high bar for any clinical outcome, there is no reason to believe that the therapy would be successful, and any actual success would be a surprising and unpredictable result.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance e or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the prevention of disease.

Conclusion

Claims 1-6, 13, 14, 16, and 22-24 are rejected. Claims 15 and 19-21 are objected to for depending from a rejected base claim but would be allowable if rewritten in independent form including all the limitations of the base claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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